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COMORBIDITY OF MOOD AND ANXIETY DISORDERS

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This article reviews data on the prevalence of panic, social phobia, generalized anxiety, and posttraumatic stress disorder, and research documenting the comorbidity of these disorders with major depression (MDD). These anxiety disorders are frequently comorbid with MDD, and 50–60% of individuals with MDD report a lifetime history of one or more of these anxiety disorders. The anxiety disorders are also highly correlated with one another, and approximately one-quarter to one-half of individuals with each of the anxiety disorders report a lifetime history of an alcohol or substance use disorder. Anxiety disorders rarely exist in isolation, with several studies reporting that over 90% of individuals with anxiety disorders have a lifetime history of other psychiatric problems. Implications for research are discussed, including the potential benefit of using combined categorical and dimensional rating scale approaches in future genetic, biochemical, neuroimaging, and treatment studies. The clinical implications of the findings are also discussed, and the results of recent clinical trials summarized. Available data suggests selective serotonin reuptake inhibitors are the first-line pharmacological treatment for these disorders, and that newer serotonin and norepinephrine reuptake inhibitors show significant promise, especially for comorbid cases. Comorbidity among depression and anxiety disorders is associated with greater symptom severity, and a considerably higher incidence of suicidality. Increased public awareness about these disorders and the availability of effective treatments is sorely needed. Depression and Anxiety, Volume 12, Supplement 1:69–76, 2000.

Key words: *depression; anxiety disorders; comorbidity*

INTRODUCTION

Major depression (MDD) and the anxiety disorders are highly prevalent and frequently comorbid diagnoses [Breier et al., 1986; Kessler et al., 1996; Fava et al., 2000]. Approximately 50–60% of individuals with a lifetime history of MDD report a lifetime history of one or more anxiety disorder, with the anxiety disorders predating the onset of MDD in the majority of cases [Kessler et al., 1996; Fava et al., 2000]. Several studies have demonstrated that comorbidity among depression and anxiety disorders is associated with greater symptom severity and persistence, more severe role impairment, increased help-seeking behavior, and higher incidence of suicidality [Angst et al., 1999; Roy-Byrne et al., 2000].

Advances in neuroscience and understandings of the neural circuits that mediate behavioral states such as fear and stress have provided new insights into the likely pathophysiology of these disorders. They have also provided a mechanism for understanding the high rates of comorbidity that exist between mood and anxiety states, and the comparable efficacy of common pharmacological agents in the treatment of these diverse conditions [Foote, 1999; Lopez et al., 1999; LeDoux, 2000].

This paper reviews data on the prevalence of panic, social phobia, generalized anxiety, and posttraumatic stress disorder, discusses rates of comorbidity of each disorder with MDD and other psychiatric disorders, and presents data on the chronological relationship among conditions. These data are summarized in Table 1. Within each anxiety disorder section, naturalistic longitudinal course data and data on the co-transmission and heritability of each disorder are also discussed. As the pure manifestation of each of the anxiety disorders is quite rare [Goisman et al., 1995], data on comorbidity among the anxiety disorders, and

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TABLE 1. Anxiety disorders: prevalence, comorbidity with MDD, and order of onset*

Diagnosis	Prevalence	Anxiety disorder comorbid with any psychiatric disorder	Anxiety disorder comorbid with MDD	MDD comorbid with anxiety disorder	Onset of anxiety disorder precedes MDD
Panic disorder	1.4%–2.9%	74%–90%	56%–73%	10%	29%
Social phobia	1.7%–3.8%	67%–92%	15%–21%	27%	65%
Generalized anxiety	1.9%–6.6%	80%–90%	62%–67%	17%	63%
Post-traumatic stress disorder	1%–13.8%	73%–83%	37%–48%	20%	53%–78%

**Data delineated in this table were derived from epidemiological studies. The citations are included in the text. MDD, Major Depressive Disorder.*

between the anxiety disorders and substance use disorders are also reviewed. Overall, the emerging picture of the course of anxiety disorders, individually and in combination with MDD, is strikingly bleak.

PANIC DISORDER

The rate of panic disorder in the general population is estimated to be between 1.4–2.9% [Dick et al., 1994a; Weissman et al., 1997; Kessler et al., 1998]. Panic disorder is a chronic condition associated with prolonged episodes of illness, low rates of full and sustained symptom remission, and high rates of relapse [Keller et al., 1994]. Within one year of patient identification, only 39% of patients with pure panic disorder achieve full symptom relief. Recovery among patients with panic disorder and agoraphobia is approximately half as likely. Individuals with panic disorder have high rates of comorbidity with mood and other disorders. Epidemiological studies estimate that 74–90% of individuals with a history of panic have met criteria for one or more other lifetime psychiatric disorder, and 56–73% have had a lifetime history of MDD [Dick et al., 1994a; Kessler et al., 1996]. Comparable rates of comorbidity between MDD and panic have been reported in clinical and epidemiological studies [Gorman and Coplan, 1996]. Approximately one-third of the time the onset of panic disorder precedes the onset of MDD, one-third of the time the onset of MDD is primary, and one-third of the time the onset of the two disorders occurs in close temporal proximity [Kessler et al., 1998; Roy-Byrne et al., 2000].

Predictors of prospective episodes of MDD among patients with panic disorder include: prior history of MDD, presence of generalized anxiety disorder (GAD), and severity of agoraphobia—with the latter two factors significant even after controlling for lifetime history of depression [Ball et al., 1994]. In one small clinic sample of patients with panic disorder, approximately 30% suffered with GAD for a median of 5 years before the onset of their panic symptoms [Garvey et al., 1988]. Consequently, it has been suggested that GAD may represent a prodrome to panic disorder in a meaningful subset of cases. There has also been a suggestion that separation anxiety disorders in childhood may represent a precursor to panic disorder [Silove et al., 1996]. Although retrospective assessment studies of adults with panic disorder support this link [Manicavasagar et al., 1998], other studies suggest early childhood separation anxiety disorder is associated with increased risk for multiple anxiety disorders and not specific to panic [Lipsitz et al., 1994], and longitudinal studies of children and adolescents fail to definitively support this association [Last et al., 1997; Hayward et al., 2000].

Clinic- [Skre et al., 1993], and population-based [Kendler et al., 1993] twin samples suggest that genetic factors contribute modestly to the etiology of panic disorder, with estimates of heritability ranging from 30–40%. A portion of this variance seems attributable to the genetic control of smothering symptoms and the tendency to experience panic attacks in response to a range of different pharmacological agents [Horwath et al., 1997; Bellodi et al., 1998; Cavallini et al., 1999]. Hypersensitivity to pharmacological agents that induce panic seems to be a unique marker for panic or anxiety disorders, and not associated with familial loading for affective illness [Balon et al., 1989; Coryell, 1997]. Although panic and MDD are frequently co-morbid, vulnerability for these two disorders seems to be inferred via unique risk factors. This suggestion is further supported by the results of family studies that report increased rates of MDD and panic in the first degree relatives of patients with these two comorbid conditions, but only increased risk of MDD in patients without comorbid panic or other anxiety disorders [Leckman et al., 1983, 1985].

SOCIAL PHOBIA

The rate of social phobia reported in the general population is estimated at 1.7–3.8% [Davidson et al., 1993; Dick et al., 1994b; Weissman et al., 1996; Faravelli et al., 2000]. Social phobia is frequently undiagnosed, with few individuals with social phobia receiving treatment unless the disorder is complicated by other comorbid conditions. Social phobia has an early age of onset, and mean duration of illness of 18 years [Reich et al., 1994]. It is estimated to precede the onset of mood and other psychiatric disorders in approximately two-thirds of all cases [Merikangas and Angst 1995; Fava et al., 2000]. Epidemiological studies estimate that 67–92% of individuals with a history of social phobia meet criteria for one or more other life-

time psychiatric disorder, and 15–21% have had a lifetime history of MDD [Weissman et al., 1996; Faravelli et al., 2000]. Higher rates of comorbidity between MDD and social phobia have been reported in clinical cohorts, with approximately 60% of patients presenting for treatment with social phobia reporting current or lifetime history of MDD [Merikangas and Angst, 1995]. Whereas the role of genetic factors in the etiology of social phobia were not supported in early smaller scale twin studies [Skre et al., 1993], results of a recent large scale population based twin study suggests genetic factors contribute to the development of social phobia, with heritability also estimated at approximately 30% [Kendler et al., 1992a]. Common genetic factors are believed to confer vulnerability for social phobia and MDD, with risk for MDD in the co-twin of individuals with social phobia significantly increased, even after controlling for comorbid depression in the proband [Kendler et al., 1992a; Merikangas and Angst, 1995]. Consistent with the results of twin studies, the first degree relatives of probands with social phobia have been found to have a 2-fold increased risk of MDD after controlling for depression in the proband [Fyer et al., 1993].

GENERALIZED ANXIETY DISORDER

Past epidemiological studies have estimated the prevalence of generalized anxiety disorder (GAD) to be between 1.9–6.6% [Wittchen et al., 1994]. More recently the rate has been estimated mid-way between these two figures at 3% [Judd et al., 1998]. Like the other anxiety disorders, GAD is highly comorbid, with approximately 80–90% of individuals who meet criteria for GAD having one or more other lifetime psychiatric disorder [Judd et al., 1998]. Approximately two-thirds of those with GAD have a lifetime history of MDD [Wittchen et al., 1994; Judd et al., 1998], with GAD having a chronologically earlier onset in 63% of all cases [Fava et al., 2000]. GAD is a chronic and disabling condition. The likelihood of remission among patients with GAD is only 0.15 after one year, and 0.25 after 2 years. Even if GAD symptom remission is achieved, the likelihood of becoming asymptomatic from all psychiatric conditions is less than 10% [Yonkers et al., 1996]. Both clinical [Skre et al., 1993] and population-based [Kendler et al., 1992b; Manicavasagar et al., 1998] studies suggest a modest contribution of genetic factors in the etiology of GAD, with genetic factors appearing to be completely shared between MDD and GAD [Kendler et al., 1992b; Manicavasagar et al., 1998]. Whether an individual develops MDD or GAD seems to depend on the unique patterning of life events, with experiences of loss associated with the onset of depression, danger precipitating the onset of anxiety, and loss and danger combined associated with the onset of comorbid mood and anxiety disorders [Brown, 1993]. The one family study conducted with GAD probands fails to support the notion that there is a shared liability between GAD and MDD, but given the assignment of diagnoses for family members were made without direct interview of relatives, the finding will require replication [Noyes et al., 1987].

POSTTRAUMATIC STRESS DISORDER

Epidemiological studies in the 1980s estimated the prevalence of posttraumatic stress disorder (PTSD) to be as low as 1% [Helzer et al., 1987]. With greater understanding of the phenomenology of the diagnoses and improvements in assessment techniques, two more recent epidemiological studies estimate the prevalence of PTSD to be in the range of 8–9% [Breslau et al., 1991; Kessler et al., 1995]. The one study that reported the rate of PTSD to be almost 14% utilized an exclusively female cohort, and rates of PTSD are approximately twice as high in females as they are in males [Breslau et al., 1997]. High risk for PTSD is reported after assaultive violence, with approximately 20% of those with these experiences developing PTSD [Breslau et al., 1998]. In one epidemiological study, combat exposure was the most frequent cause of PTSD among men, and sexual molestation and rape were the most frequent precipitants of PTSD in women [Kessler et al., 1995]. In another epidemiological study, sudden unexpected death of a loved one was the most common precipitating event of persons with PTSD (31% of all PTSD cases), an event experienced by 60% of the sample and associated with PTSD in 14% of those exposed [Breslau et al., 1998].

Like MDD and many of the anxiety disorders, PTSD is often a chronic and recurring disorder [Ballenger et al., 2000]. Slightly over one-third of individuals with PTSD fail to recover after many years, with even higher rates of chronicity evident among clinic referred cases [Kessler et al., 1995]. Among those who present with a chronic episode of PTSD, the likelihood of recovering is only 18% within 5 years [Zlotnick et al., 1999]. Risk factors for chronicity include: female gender, history of early separation, pre-existing anxiety disorder, family history of anxiety disorders, and family history of antisocial personality disorder, which is likely also a proxy for early family adversity [Breslau et al., 1991].

Approximately three-quarters of individuals with PTSD experience one or more comorbid lifetime diagnosis, and 37–48% report a lifetime history of MDD [Breslau et al., 1991, 1997; Kessler et al., 1995]. In one-half to three-quarter of all cases, the onset of PTSD is primary. The risk for MDD after PTSD is about the same as the risk of MDD after any other anxiety disorder, and 30–40% more likely in individuals with history of a pre-existing anxiety disorder [Breslau

et al., 1997]. Prior twin studies suggest that there are significant genetic influences on symptom liability in PTSD, with genetic factors accounting for 13–30% of the variance in re-experiencing symptoms, 30—34% for symptoms in the avoidance cluster, and 28–32% for the arousal symptoms [True et al., 1993]. Family studies suggest a shared liability for PTSD and MDD, with familial loading for MDD predicting chronic PTSD in trauma survivors [Davidson et al., 1998].

COMORBIDITY AMONG ANXIETY DISORDERS AND BETWEEN SUBSTANCE USE AND ANXIETY DISORDERS

In addition to being highly comorbid with mood disorders, the individual anxiety disorders are highly comorbid with one another. Table 2 outlines the rates of comorbidity among the different anxiety disorders reported in prior epidemiological studies [Dick et al., 1994a,b; Wittchen et al., 1994; Kessler et al., 1995]. These rates are roughly comparable to the rates reported in a recent study of 711 treatment seeking patients participating in a multi-center, longitudinal naturalistic study of anxiety disorders [Goisman et al., 1995]. Within this clinical cohort, only 49% met criteria for one index anxiety diagnoses at intake, 17% had no other current psychiatric disorder, and less than 10% had no other lifetime history of psychopathology [Goldenberg et al., 1996]. Current and lifetime comorbidity among the anxiety disorders, and between the anxiety disorders and other psychiatric conditions, is the rule, with pure anxiety states rare and relatively uncommon.

Also frequently comorbid with anxiety disorders are alcohol and substance abuse disorders. Epidemiological studies estimate that 35–54% of individuals with an anxiety disorder have a lifetime diagnosis of an alcohol use disorder. The rate of alcohol abuse among individuals with PTSD is approximately twice as high in males than females (52% vs. 28%) [Kessler et al., 1995]. Epidemiological studies also estimate that as many as 24–43% of individuals with anxiety disorders have a lifetime history of a substance use disorder [Dick et al., 1994a,b; Wittchen et al., 1994; Kessler et al., 1995]. Comparable rates of alcohol and substance use disorders have been reported in clinical studies. In slightly over 60% of all comorbid cases identified in the previously cited multi-center cohort of patients with anxiety disorders, alcohol and substance use disorders were found to emerge on average 10 or more years after the onset of the primary anxiety disorder [Goldenberg et al., 1995].

TABLE 2. Lifetime comorbidity with other anxiety, alcohol, and substance use disorders*

	Index diagnoses			
	Panic	Social phobia	GAD	PTSD
Panic	—	14%	24%	7%
Social phobia	20%	—	34%	28%
GAD	25%	27%	—	17%
PTSD	9%	15%	13%	—
Alcohol abuse	54%	35%	37%	35%
Substance abuse	43%	24%	27%	29%

**Data delinated in this table were derived from epidemiological studies. The citations are included in the text. GAD, Generalized Anxiety Disorder; PTSD, Posttraumatic Stress Disorder.*

COMORBIDITY DATA: SUMMARY OF RESEARCH FINDINGS

The rate of comorbidity reported between anxiety, mood, and other psychiatric or substance use disorders is significantly greater than one would expect by chance, given the relative low prevalence of the different diagnoses. The majority of cases of anxiety disorders have a lifetime history of other psychiatric problems, with comorbidity rates exceeding 90% in several studies. Anxiety disorders are frequently comorbid with MDD, and 50–60% of individuals with MDD report a lifetime history of an anxiety disorder. In one-half to three-quarter of all cases of social phobia, GAD, and PTSD, the onset of the anxiety disorder precedes the onset of MDD. In contrast, panic disorder is about equally likely to onset before, after, or simultaneously with MDD. All of the anxiety disorders seem to have modest heritability, in the range of 30%. Twin or family studies suggest the liability for MDD is shared with social phobia, GAD, and PTSD. The liability for panic disorder and MDD seems to be relatively independent, however, with propensity to experience smothering symptoms and hypersensitivity to pharmacological agents that induce panic attacks conferring a unique vulnerability for panic or anxiety disorders. In addition, the anxiety disorders are highly correlated with one another, and approximately one-quarter to one-half of individuals with each of the anxiety disorders report a lifetime history of an alcohol or substance use disorder.

RESEARCH IMPLICATIONS

Comorbidity has been largely ignored in prior research [Caron and Rutter, 1991]. As Caron and Rutter [1991] highlighted, given the high rates of comorbidity among psychiatric disorders, this can be very problematic, as the findings associated with condition X may actually be a consequence of condition Y. Furthermore, they noted, assuming X is the same in the presence or absence of Y may be erroneous. As noted, it may be possible that the comorbid pattern constitutes a meaningful subgroup of patients with condition X, as for example, has been demonstrated in the case of MDD with comorbid conduct disorder in child onset cases. When compared to depressed children

without comorbid conduct disorder, those with conduct disorder have lower rates of MDD in first- and second-degree relatives, decreased rates of MDD recurrence, and a higher incidence of antisocial personality disorder in adulthood. Systematic reporting of, and secondary analyses using the comorbid diagnostic profile of research participants is clearly warranted in future research investigations. An alternate strategy would be to select 'pure' diagnostic groups for study, but this is not recommended as it will result in non-representative, clinically non-meaningful, samples.

There are multiple potential meanings to the high rates of comorbidity among the mood and anxiety disorders [Caron and Rutter, 1991]. Anxiety disorders may: constitute an early manifestation of mood disorders, represent alternative manifestations of MDD, increase the hazard for the onset of MDD, or be unique conditions which are highly comorbid due to shared risk (genetic or environmental) factors. At present it is not feasible to choose among these alternatives.

The reason for the high rates of comorbidity between mood and anxiety disorders will likely be better understood when the mechanisms responsible for the links are better understood. For example, diabetes is a disease that is associated with both short-term and long-term complications. In the short-term, blood sugar changes associated with diabetes can lead to ketoacidosis or hypoglycemia. Excessive glucose levels in the blood over years can lead to vision loss, kidney and heart disease, hypertension and stroke, neuropathy and vascular disease, and skin and teeth problems. These disparate medical conditions are understood to derive from the primary disorder of diabetes because the mechanisms are well understood. At some point in time, the disparate conditions associated with anxiety disorders may be more clearly understood from a mechanistic perspective. It is currently unclear if early identification and treatment of anxiety disorders could prevent the onset of mood disorders. This is an area of research that warrants further investigation.

Given the high comorbidity among the anxiety disorders themselves, dimensional traits such as neuroticism and anxious temperament (e.g., behavioral inhibition) have been proposed as alternatives to categorical approaches for defining these psychiatric phenotypes [Smoller and Tsuang, 1998]. There is emerging evidence that both genetic factors and early adverse experiences can influence dimensional personality traits [Carey and DiLalla, 1994; Foote, 1999]. Available data suggests, however, that constructs like behavioral inhibition only constrain the probability for, and do not guarantee, the eventual onset of anxiety syndromes [Kagan and Snidman, 1999]. More research is needed to understand how these personality traits interact with other factors to confer vulnerability to psychopathology. The utilization of animal models will provide a valuable venue to dissect the genetic and environmental factors that influence the onset of mood and anxiety disorders [Charney and Deutch, 1996; Foote, 1999]. In addition, the use of categorical diagnostic approaches and dimensional rating scales in tandem will facilitate identification of meaningful phenotypes for future genetic, biochemical, neuroimaging, and treatment studies.

TREATMENT IMPLICATIONS

One of the key treatment implications of the research reviewed in this manuscript is the importance of surveying symptoms associated with depression and multiple anxiety disorders in patients who present with one primary set of mood or anxiety complaints. In all likelihood, the patient is experiencing significant symptomatology from one or more comorbid diagnostic conditions. Given the high comorbidity between PTSD and MDD, and PTSD and the other anxiety disorders, a careful survey of trauma experiences is also indicated, as patients will often not disclose trauma histories unless specifically queried [Dill et al., 1991]. It is important to note that in one of the recent epidemiological surveys, sudden unexpected death of a loved one was the most common precipitating event of persons with PTSD (31% of all PTSD cases), an event experienced by 60% of the sample and associated with PTSD in 14% of those exposed [Breslau et al., 1998]. Therefore, careful inquiry about recent losses and the manner in which the loved one's death was learned about is also indicated. In addition, suicide risk is significantly elevated in depressed patients with comorbid anxiety disorders, highlighting the need for systematic assessment and monitoring of these symptoms as well. Also, given the high co-occurrence of alcohol and substance use disorders in patients with mood and anxiety diagnoses, assessment of these disorders and use of appropriate adjunctive clinical interventions to target substance use problems is imperative (e.g., Alcoholics and Narcotics Anonymous).

As recently reviewed [Ballenger, 1999], there are a range of classes of pharmacological agents with proven efficacy in the treatment of anxiety disorders. Double-blind placebo-controlled trials have demonstrated the efficacy of tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), and benzodiazepines in the treatment of panic and PTSD, and data to support the use of these agents in social phobia and GAD exist as well. Given the side effects profile and risk of lethality in overdose with TCAs, the dietary restrictions associated with MAOIs, and the problems with withdrawal symptoms and the lack of anti-depressant effects with benzodiazepines, these agents are not considered primary treatments for anxiety disorders, particularly when comorbid with MDD.

Selective serotonin re-uptake inhibitors (SSRI) have become the first-line treatment for depression and anxiety disorders [Ballenger, 1999]. The SSRIs paroxetine, fluvoxamine, citalopram, fluoxetine, and sertraline have been shown to have demonstrated efficacy in the treatment of depression and panic disorder, with

subsets of these medications also found to be effective in the treatment of social phobia, GAD, and PTSD. When used to treat patients with comorbid mood and anxiety disorders, higher doses of SSRI medications are often required.

Venlafaxine, a newer antidepressant with serotonergic and norepinephrine re-uptake inhibition (SNRI) properties, has been found to be an effective treatment for GAD in five placebo-controlled clinical trials [Ballenger, 1999; Sheehan, 1999]. In studies with depressed patients, venlafaxine has also been found to significantly decrease anxiety in addition to depressive symptoms [Khan et al., 1998; Rudolph et al., 1998]. In one study that compared the efficacy of the SSRI fluoxetine and the SNRI venlafaxine, venlafaxine was found to be superior to fluoxetine in improving anxiety symptoms in patients with depression [Silverstone and Ravindran, 1999]. Given the importance of the adrenergic and the serotonergic systems in the pathophysiology of mood and anxiety disorders demonstrated in preclinical and clinical studies, venlafaxine may emerge as a first-line treatment for patients with comorbid mood and anxiety disorders with further study.

Nefazodone, a newer antidepressant which is a 5-HT_2 antagonist, has also been found to be effective in the treatment of depression, social phobia, and PTSD, with a multi-center trial for the treatment of panic disorder currently underway [Ballenger, 1999; Gorman and Kent, 1999]. Newer classes of medications, like reversible inhibitors of monoamine oxidase A (RIMA), that are not yet available in the United States [Davidson, 2000], and corticotropin releasing hormone type 1 receptor antagonists, that are still under development [Nemeroff, 1996; Arborelius et al., 1999; Holsboer, 1999], will likely also emerge to have a role in the treatment of depression, anxiety disorders, and their copresentation. In addition, for patients with PTSD who have frequent problems with angry outbursts and impulsivity, anticonvulsants are emerging as an important adjunctive treatment [Ballenger, 1999].

In addition to pharmacological interventions, specialized psychotherapies have been developed for the treatment of depression and each of the anxiety disorders [Shear and Beidel, 1998; Ballenger, 1999; Foa, 2000;]. Each involves a combination of exposure, cognitive restructuring, and in some cases, social effectiveness and relaxation training. Although pharmacological and psychotherapeutic interventions seem to be roughly comparable in the short-term treatment of mood and anxiety disorders, there is some evidence that greater relapse prevention is achieved with the cognitive behavioral therapies (CBT) [Ballenger, 1999]. In addition, in a recent multi-center clinical trial of nefazodone and CBT in adult depression, the combined treatment was found to be superior to medication or psychotherapy alone [Keller et al., 2000]. More combined treatment trials are needed, with clinical improvement for comorbid cases to be measured with a decline in depression and anxiety symptoms, and a restoration of functioning, that is so frequently significantly impaired in those with comorbid mood and anxiety disorders [Ballenger et al., 1999].

CONCLUSION

Over the last 5 years there has been significant progress in the assessment, diagnosis, and treatment of mood and anxiety disorders. The comorbid nature of these disorders, and their frequent chronic and debilitating course has been extensively documented. With recent advances in neuroscience, pharmacological developments, and psychotherapeutic research, there is considerable hope in the future for patients inflicted with these disorders. Greater public awareness about these disorders and the availability of effective treatments is sorely needed.

REFERENCES

Angst J, Angst F, Stassen HH. 1999. Suicide risk in patients with major depressive disorder. J Clin Psychiatry 60(Suppl):57–62; 75–76; 113–116.

Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. 1999. The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol 160:1–12.

Ball SG, Otto MW, Pollack MH, Rosenbaum JF. 1994. Predicting prospective episodes of depression in patients with panic disorder: a longitudinal study. J Consult Clin Psychol 62:359–365.

Ballenger JC. 1999. Current treatments of the anxiety disorders in adults. Biol Psychiatry 46:1579–1594.

Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Foa EB, Kessler RC, McFarlane AC, Shalev AY. 2000. Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry 61(Suppl): 60–66.

Ballenger JC, Feighner JP, Entsuah AR, McPherson MK. 1999. Clinical guidelines for establishing remission in patients with depression and anxiety. Efficacy of once-daily venlafaxine extended release (XR) for symptoms of anxiety in depressed outpatients. J Clin Psychiatry 60(Suppl):29–34.

Balon R, Jordan M, Pohl R, Yeragani VK. 1989. Family history of anxiety disorders in control subjects with lactate-induced panic attacks. Am J Psychiatry 146:1304–1306.

Bellodi L, Perna G, Caldirola D, Arancio C, Bertani A, Di Bella D. 1998. CO_2-induced panic attacks: a twin study. Am J Psychiatry 155:1184–1188.

Breier A, Charney DS, Heninger GR. 1986. Agoraphobia with panic attacks. Development, diagnostic stability, and course of illness. Arch Gen Psychiatry 43:1029–1036.

Breslau N, Davis GC, Andreski P, Peterson E. 1991. Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen Psychiatry 48:216–222.

Breslau N, Davis GC, Peterson EL, Schultz L. 1997. Psychiatric sequelae of posttraumatic stress disorder in women. Arch Gen Psychiatry 54:81–87.

Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P. 1998. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. Arch Gen Psychiatry 55:626–632.

Brown GW. 1993. Life events and affective disorder: replications and limitations. Psychosom Med 55:248–259.

Carey G, DiLalla DL. 1994. Personality and psychopathology: genetic perspectives. J Abnorm Psychol 103:32–43.

Caron C, Rutter M. 1991. Comorbidity in child psychopathology: concepts, issues and research strategies. J Child Psychol Psychiatry 32:1063–1080.

Cavallini MC, Perna G, Caldirola D, Bellodi L. 1999. A segregation study of panic disorder in families of panic patients responsive to the 35% CO_2 challenge. Biol Psychiatry 46:815–820.

Charney DS, Deutch A. 1996. A functional neuroanatomy of anxiety and fear: implications for the pathophysiology and treatment of anxiety disorders. Crit Rev Neurobiol 10:419–446.

Coryell W. 1997. Hypersensitivity to carbon dioxide as a disease-specific trait marker. Biol Psychiatry 41:259–263.

Davidson JR. 2000. Pharmacotherapy of posttraumatic stress disorder: treatment options, long-term follow-up, and predictors of outcome. J Clin Psychiatry 61(Suppl):52–56; 57–59.

Davidson JR, Hughes DL, George LK, Blazer DG. 1993. The epidemiology of social phobia: findings from the Duke Epidemiological Catchment Area Study. Psychol Med 23:709–718.

Davidson JR, Tupler LA, Wilson WH, Connor KM. 1998. A family study of chronic post-traumatic stress disorder following rape trauma. J Psychiatr Res 32:301–309.

Dick CL, Bland RC, Newman SC. 1994a. Epidemiology of psychiatric disorders in Edmonton. Panic disorder. Acta Psychiatr Scand Suppl 376:45–53.

Dick CL, Sowa B, Bland RC, Newman SC. 1994b. Epidemiology of psychiatric disorders in Edmonton. Phobic disorders. Acta Psychiatr Scand Suppl 376:36–44.

Dill DL, Chu JA, Grob MC, Eisen SV. 1991. The reliability of abuse history reports: a comparison of two inquiry formats. Comp Psychiatry 32:166–169.

Faravelli C, Zucchi T, Viviani B, Salmoria R, Perone A, Paionni A, Scarpato A, Vigliaturo D, Rosi S, D'adamo D, Bartolozzi D, Cecchi C, Abrardi L. 2000. Epidemiology of social phobia: a clinical approach. Eur Psychiatry 15:17–24.

Fava M, Rankin MA, Wright EC, Alpert JE, Nierenberg AA, Pava J, Rosenbaum JF. 2000. Anxiety disorders in major depression. Comp Psychiatry 41:97–102.

Foa EB. 2000. Psychosocial treatment of posttraumatic stress disorder. J Clin Psychiatry 61(Suppl):43–48; 49–51.

Foote SL. 1999. Development and vulnerability: new perspectives for anxiety disorders [editorial]. Biol Psychiatry 46:1457–1460.

Fyer AJ, Mannuzza S, Chapman TF, Liebowitz MR, Klein DF. 1993. A direct interview family study of social phobia. Arch Gen Psychiatry 50:286–293.

Garvey MJ, Cook B, Noyes R Jr. 1988. The occurrence of a prodrome of generalized anxiety in panic disorder. Comp Psychiatry 29:445–449.

Goisman RM, Goldenberg I, Vasile RG, Keller MB. 1995. Comorbidity of anxiety disorders in a multicenter anxiety study. Comp Psychiatry 36:303–311.

Goldenberg IM, Mueller T, Fierman EJ, Gordon A, Pratt L, Cox K, Park T, Lavori P, Goisman RM, Keller MB. 1995. Specificity of substance use in anxiety-disordered subjects. Comp Psychiatry 36:319–328.

Goldenberg IM, White K, Yonkers K, Reich J, Warshaw MG, Goisman RM, Keller MB. 1996. The infrequency of "pure culture" diagnoses among the anxiety disorders. J Clin Psychiatry 57:528–533.

Gorman JM, Coplan JD. 1996. Comorbidity of depression and panic disorder. J Clin Psychiatry 57(Suppl):34–41; 42–43.

Gorman JM, Kent JM. 1999. SSRIs and SMRIs: broad spectrum of efficacy beyond major depression. J Clin Psychiatry 60(Suppl): 33–38; 39.

Hayward C, Killen JD, Kraemer HC, Taylor CB. 2000. Predictors of panic attacks in adolescents. J Am Acad Child Adolesc Psychiatry 39:207–214.

Helzer JE, Robins LN, McEvoy L. 1987. Post-traumatic stress disorder in the general population. Findings of the epidemiologic catchment area survey. N Engl J Med 317:1630–1634.

Holsboer F. 1999. The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. J Psychiatr Res 33:181–214.

Horwath E, Adams P, Wickramaratne P, Pine D, Weissman MM. 1997. Panic disorder with smothering symptoms: evidence for increased risk in first-degree relatives. Depress Anxiety 6:147–153.

Judd LL, Kessler RC, Paulus MP, Zeller PV, Wittchen HU, Kunovac JL. 1998. Comorbidity as a fundamental feature of generalized anxiety disorders: results from the National Comorbidity Study (NCS). Acta Psychiatr Scand Suppl 393:6–11.

Kagan J, Snidman N. 1999. Early childhood predictors of adult anxiety disorders. Biol Psychiatry 46:1536–1541.

Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J. 2000. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression [see comments]. N Engl J Med 342:1462–1470.

Keller MB, Yonkers KA, Warshaw MG, Pratt LA, Gollan JK, Massion AO, White K, Swartz AR, Reich J, Lavori PW. 1994. Remission and relapse in subjects with panic disorder and panic with agoraphobia: a prospective short-interval naturalistic follow-up. J Nerv Ment Dis 182:290–296.

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. 1992a. The genetic epidemiology of phobias in women. The interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. Arch Gen Psychiatry 49:273–281.

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. 1992b. Major depression and generalized anxiety disorder. Same genes, (partly) different environments? Arch Gen Psychiatry 49:716–722.

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. 1993. Panic disorder in women: a population-based twin study [see comments]. Psychol Med 23:397–406.

Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. 1996. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey [see comments]. Br J Psychiatry Suppl 17–30.

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. 1995. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52:1048–1060.

Kessler RC, Stang PE, Wittchen HU, Ustun TB, Roy-Burne PP, Walters EE. 1998. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Arch Gen Psychiatry 55: 801–808.

Khan A, Upton GV, Rudolph RL, Entsuah R, Leventer SM. 1998. The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. Venlafaxine Investigator Study Group. J Clin Psychopharmacol 18:19–25.

Last CG, Hansen C, Franco N. 1997. Anxious children in adulthood: a prospective study of adjustment. J Am Acad Child Adolesc Psychiatry 36:645–652.

Leckman JF, Weissman MM, Merikangas KR, Pauls DL, Prusoff BA. 1983. Panic disorder and major depression. Increased risk of depression, alcoholism, panic, and phobic disorders in families of depressed probands with panic disorder. Arch Gen Psychiatry 40:1055–1060.

Leckman JF, Weissman MM, Merikangas KR, Pauls DL, Prusoff BA, Kidd KK. 1985. Major depression and panic disorder: a family study perspective. Psychopharmacol Bull 21:543–545.

LeDoux JE. 2000. Emotion circuits in the brain [In Process Citation]. Annu Rev Neurosci 23:155–184.

Lipsitz JD, Martin LY, Mannuzza S, Chapman TF, Liebowitz MR, Klein DF, Fyer AJ. 1994. Childhood separation anxiety disorder in patients with adult anxiety disorders. Am J Psychiatry 151: 927–929.

Lopez JF, Akil H, Watson SJ. 1999. Neural circuits mediating stress. Biol Psychiatry 46:1461–1471.

Manicavasagar V, Silove D, Hadzi-Pavlovic D. 1998. Subpopulations of early separation anxiety: relevance to risk of adult anxiety disorders. J Affect Disord 48:181–190.

Merikangas KR, Angst J. 1995. Comorbidity and social phobia: evidence from clinical, epidemiologic, and genetic studies. Eur Arch Psychiatry Clin Neurosci 244:297–303.

Nemeroff CB. 1996. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions [see comments]. Mol Psychiatry 1:336–342.

Noyes R Jr, Clarkson C, Crowe RR, Yates WR, McChesney CM. 1987. A family study of generalized anxiety disorder. Am J Psychiatry 144:1019–1024.

Reich J, Goldenberg I, Goisman R, Vasile R, Keller M. 1994. A prospective, follow-along study of the course of social phobia: II. Testing for basic predictors of course. J Nerv Ment Dis 182:297–301.

Roy-Byrne PP, Stang P, Wittchen HU, Ustun B, Walters EE, Kessler RC. 2000. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Association with symptoms, impairment, course and help-seeking. Br J Psychiatry 176:229–235.

Rudolph RL, Entsuah R, Chitra R. 1998. A meta-analysis of the effects of venlafaxine on anxiety associated with depression. J Clin Psychopharmacol 18:136–144.

Shear MK, Beidel DC. 1998. Psychotherapy in the overall management strategy for social anxiety disorder. J Clin Psychiatry 59(Suppl):39–46.

Sheehan DV. 1999. Venlafaxine extended release (XR) in the treatment of generalized anxiety disorder. J Clin Psychiatry 60 (Suppl):23–28.

Silove D, Manicavasagar V, Curtis J, Blaszczynski A. 1996. Is early separation anxiety a risk factor for adult panic disorder?: a critical review. Comp Psychiatry 37:167–179.

Silverstone PH, Ravindran A. 1999. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group [see comments]. J Clin Psychiatry 60:22–28.

Skre I, Onstad S, Torgersen S, Lygren S, Kringlen E. 1993. A twin study of DSM-III-R anxiety disorders. Acta Psychiatr Scand 88:85–92.

Smoller JW, Tsuang MT. 1998. Panic and phobic anxiety: defining phenotypes for genetic studies [see comments]. Am J Psychiatry 155:1152–1162.

True WR, Rice J, Eisen SA, Heath AC, Goldberg J, Lyons MJ, Nowak J. 1993. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms [see comments]. Arch Gen Psychiatry 50:257–264.

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lepine JP, Newman SC, Oakley-Browne MA, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen HU, Yeh EK. 1997. The cross-national epidemiology of panic disorder. Arch Gen Psychiatry 54:305–309.

Weissman MM, Bland RC, Canino GJ, Greenwald S, Lee CK, Newman SC, Rubio-Stipec M, Wickramaratne PJ. 1996. The cross-national epidemiology of social phobia: a preliminary report. Int Clin Psychopharmacol 11 Suppl 3:9–14.

Wittchen HU, Zhao S, Kessler RC, Eaton WW. 1994. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry 51:355–364.

Yonkers KA, Warshaw MG, Massion AO, Keller MB. 1996. Phenomenology and course of generalized anxiety disorder. Br J Psychiatry 168:308–313.

Zlotnick C, Warshaw M, Shea MT, Allsworth J, Pearlstein T, Keller MB. 1999. Chronicity in posttraumatic stress disorder (PTSD) and predictors of course of comorbid PTSD in patients with anxiety disorders. J Trauma Stress 12:89–100.